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FUNGAL PATHOGENESIS

Host modulation every which way

The plant pathogenic fungus *Fusarium oxysporum* secretes an effector that is similar to a plant peptide hormone, underscoring the variety of mechanisms that plant pathogens have evolved to tamper with host physiology.

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Plant pathogens cause devastating diseases of crop plants and threaten food security in an era of continuous population growth. Annual losses due to fungal and oomycete diseases amount to enough food calories to feed at least half a billion people[1]. Understanding how plant pathogens infect and colonize plants should help to develop disease-resistant crops. It appears that plant pathogens are sophisticated manipulators of their hosts. They secrete effector molecules that alter host biological processes in a variety of ways, generally promoting the pathogen lifestyle[2]. A new study by Masachis, Segorbe and colleagues[3] describes a new mechanism by which plant pathogens interfere with plant physiology. They discovered that the root-infecting fungus *F. oxysporum* secretes a peptide similar to the plant regulatory peptide RALF (rapid alkalinization factor) to induce host tissue alkalinization and enhance plant colonization. This study demonstrates that in addition to secreting classical plant hormones (or mimics thereof)[4], fungi have also evolved functional homologues of plant peptides to alter host cellular processes.

Much research on plant pathogen effectors has focused on proteins translocated to the host cell but other classes do occur[2]. Some effector proteins function in the extracellular space between the microorganism and host, thereby modulating biological processes at the cell surface or apoplast of the plant. Other effectors are microbially produced metabolites. In particular, pathogenic fungi are known to secrete plant hormones or compounds that mimic plant hormones, enabling the microorganism to hijack host defence, metabolism, and development[4]. For instance, a recent study showed that production of the plant hormone cytokinin by the rice blast fungus *Magnaporthe oryzae* contributes to virulence by dampening host defences and altering nutrient distribution at the infection site[5].

Fungal infection of plants is often associated with changes in the extracellular pH of the host tissue[6,7]. Masachis, Segorbe and colleagues determined that extracellular alkalinization enhances the virulence of

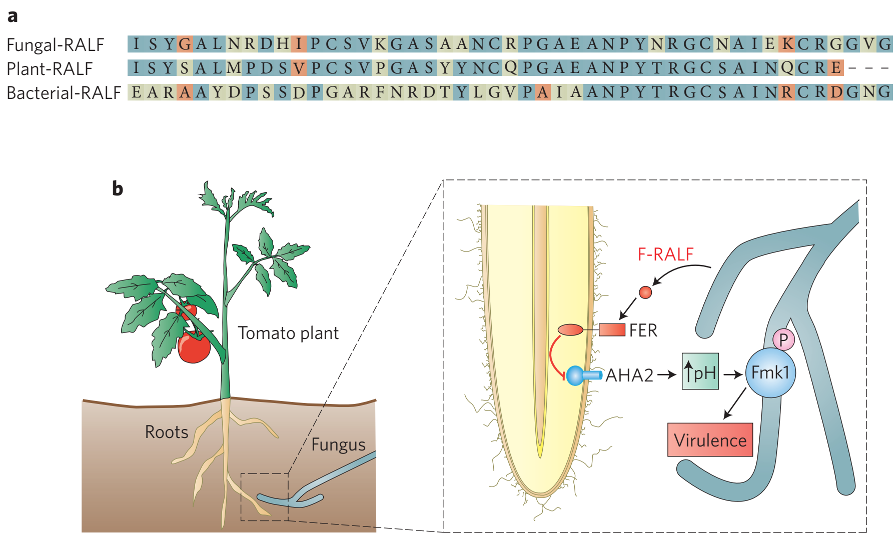

Figure 1 | *Fusarium oxysporum* secretes a RALF peptide to induce extracellular alkalinization of plant roots. **a**, Multiple sequence alignment of RALF peptides from a fungus (*Fusarium oxysporum* f. sp. *lycopersici* 4287, GenBank accession KNB14556), a plant (*Zea mays*, NP_001149642), and a bacterium (*Streptomyces acidiscabies*, WP_010351089). **b**, Schematic illustration of the effect of *F. oxysporum*-secreted F-RALF. The peptide co-opts the plant receptor kinase FERONIA (FER), which signals to block the plasma membrane H^+-ATPase 2 (AHA2)[9], thereby increasing the extracellular pH of host root tissue as well as fungal virulence toward the plant.

F. oxysporum toward tomato plants. This increase in pH leads to the activation of a conserved fungal mitogen-activated protein kinase (MAPK), named Fmk1, which is required for fungal pathogenicity. This prompted them to identify the trigger of this fungus-driven alkalinization. Unexpectedly, they observed that the *F. oxysporum* genome encodes a peptide with sequence similarity to the plant peptide hormone RALF, which is known to increase extracellular alkalization[8]. Interestingly, whereas plant RALFs peptides are produced upon cleavage of a pro-peptide by a secreted protease, the fungal RALF does not carry a pro-peptide region, indicating that it has evolved to be active independent of plant- or fungus-mediated enzymatic processing. F-RALF, a synthetic peptide matching the *F. oxysporum* sequence, had similar alkalinization-inducing activity in tomato as a plant RALF peptide. Genetic analyses indicated that F-RALF is important for *F. oxysporum* colonization of tomato. F-RALF seems to signal through the plant receptor kinase FERONIA (FER), which was recently identified as the RALF receptor[9]. An *Arabidopsis* mutant with a defective FER failed to respond to F-RALF and displayed enhanced resistance to *F. oxysporum*. The emerging picture is that F-RALF has co-opted FER to induce extracellular alkalinization of plant roots, enabling infection (Fig. 1).

Masachis, Segorbe and colleagues[3] proposed that FER negatively regulates plant immunity, based on the observations that *Arabidopsis fer* mutant plants constitutively express immune genes and are more resistant to a *F. oxysporum* strain pathogenic on *Arabidopsis*. However, the resistance phenotype of the *fer* mutant can also be explained by the requirement of *F. oxysporum* to increase extracellular pH — a process mediated by the perception of

F-RALF by FER. Thus, the F-RALF effect on FER could be explained by host tissue alkalinization, without evoking a direct effect on plant immunity. Furthermore, the 'autoimmune' phenotype of *fer* mutant plants does not necessarily imply that FER is normally involved in the negative regulation of plant immunity, as recently discussed for other plant components[10]. Thus, the actual function of FER and endogenous RALF peptides in immunity remains to be studied in more depth.

The authors found that the 40–70 amino-acid RALF domain is widely distributed, with over 70 proteins identified in fungi and about another 60 from various eukaryotic and a few bacterial species, in addition to the ~1400 sequences from plants[3] (Fig. 1). Despite earlier reports of horizontal gene transfer[11], Masachis, Segorbe and colleagues[3] could not discriminate between alternative evolutionary scenarios because the short size and high sequence diversification of the RALF domain precluded the generation of well-supported phylogenies. Interestingly, RALF peptides can be detected in bacteria, notably in *Streptomyces* species that are associated with plants. One such species is *Streptomyces acidiscabies*, the causal agent of the potato scab disease[12]. Remarkably, this acid-tolerant bacterium is notable for causing potato scab in soils of pH lower than 5.2 (ref. 12) raising the possibility that *S. acidiscabies* secretes a RALF-like peptide to modulate the extracellular pH of its host plants.

Plant pathogens have evolved an extraordinarily diverse repertoire of effector molecules to modulate an ever-growing list of biological process in their hosts. Masachis, Segorbe and colleagues[3] have uncovered yet another mechanism by which pathogen effectors target a key pathway in plants. Future work will reveal the degree to which other plant pathogens besides *F. oxysporum* secrete RALF-like peptides to modulate host physiology. ❐

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